Providing Regulatory Submissions in Electronic Format - NDA

NDA submissions divided into three parts

1. Archival copy -entire NDA in electronic format

2. Review copy -portions of the NDA as paper desk copy

3. Review aids -desk copy (data sets, word processing files)

NDA is a collection of individual documents

Convert each document into a PDF file

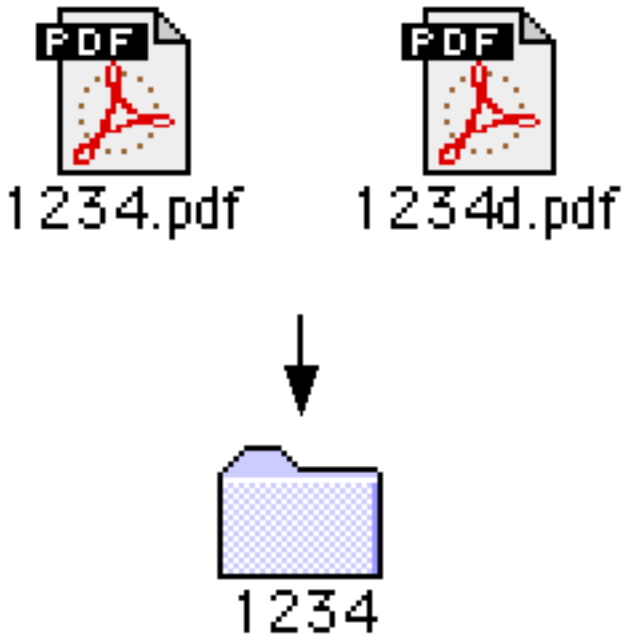
For example

Overall summary for the NDA (item 2 on FDA form 356h)

summary.pdf

For example
Pharmtox study report
Two files

- **individual animal line listings (1234d.pdf)**
- **rest of the study report (1234.pdf)**


PDF
1234.pdf
PDF
1234d.pdf
1234

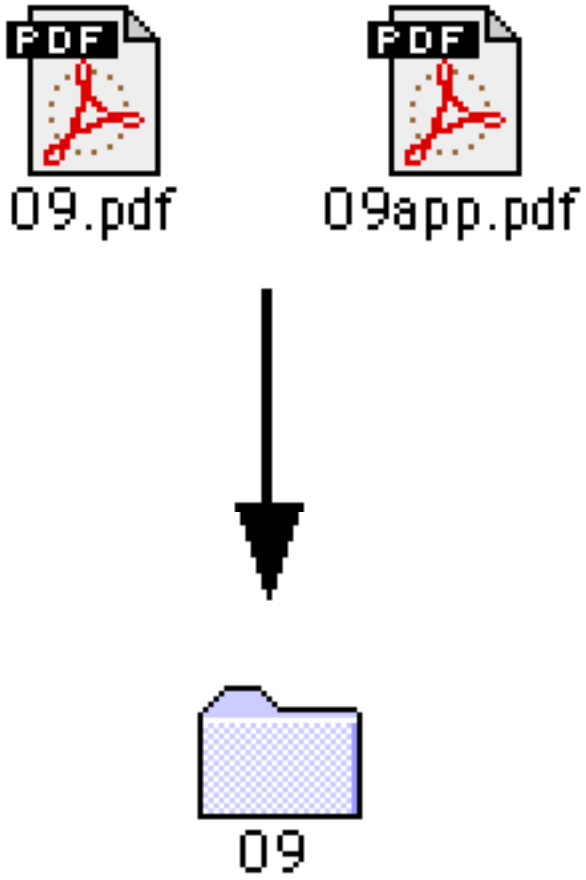
For example
Clinical study reports

One study = one pdf file

Clinical study reports

or one study provided in two pdf files

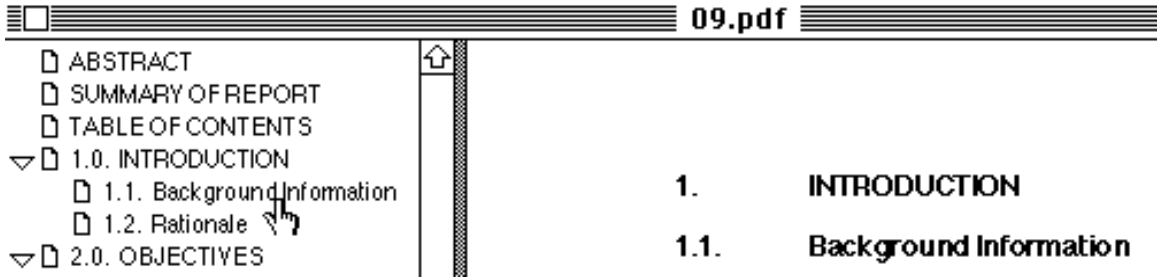
- **study report, protocol and sample CRF (09.pdf)**
- **the remaining appendices (09app.pdf)**


PDF
09.pdf
PDF
09app.pdf
09

For each document provide
Bookmarks for each section of the document's table of contents

TABLE OF CONTENTS

Bookmarks

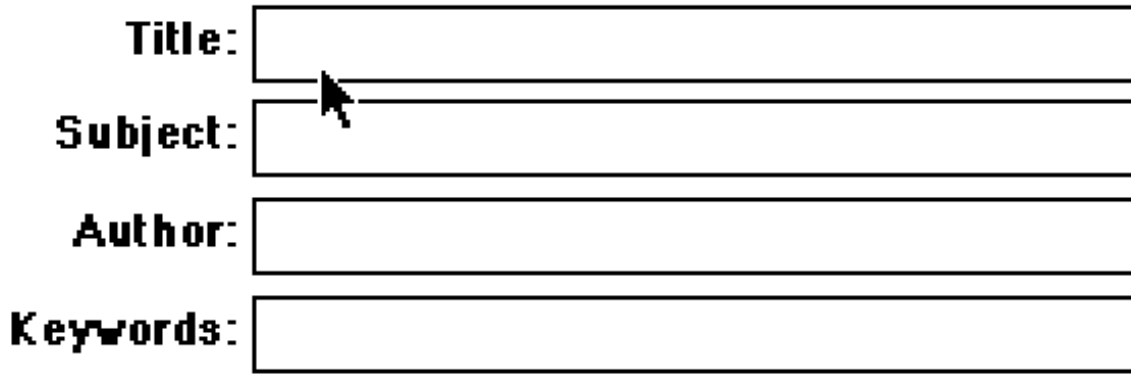

09.pdf
ABSTRACT
SUMMARY OF REPORT
TABLE OF CONTENTS
1.0. INTRODUCTION
1.1. Background Information
1.2. Rationale
2.0. OBJECTIVES
1. INTRODUCTION
1.1. Background Information

For each document provide
Hypertext linking to
- annotations
- related sections
- references
- appendices
- tables
- figures

not located on the same page

Regulatory clearance for the study was obtained from each c
before the start of the study. Details of the regulatory authorities
participating country are provided in Appendix 3.

For each document
Identify the document in the PDF Document information Title field



Now NDA is a collection of individual files with:

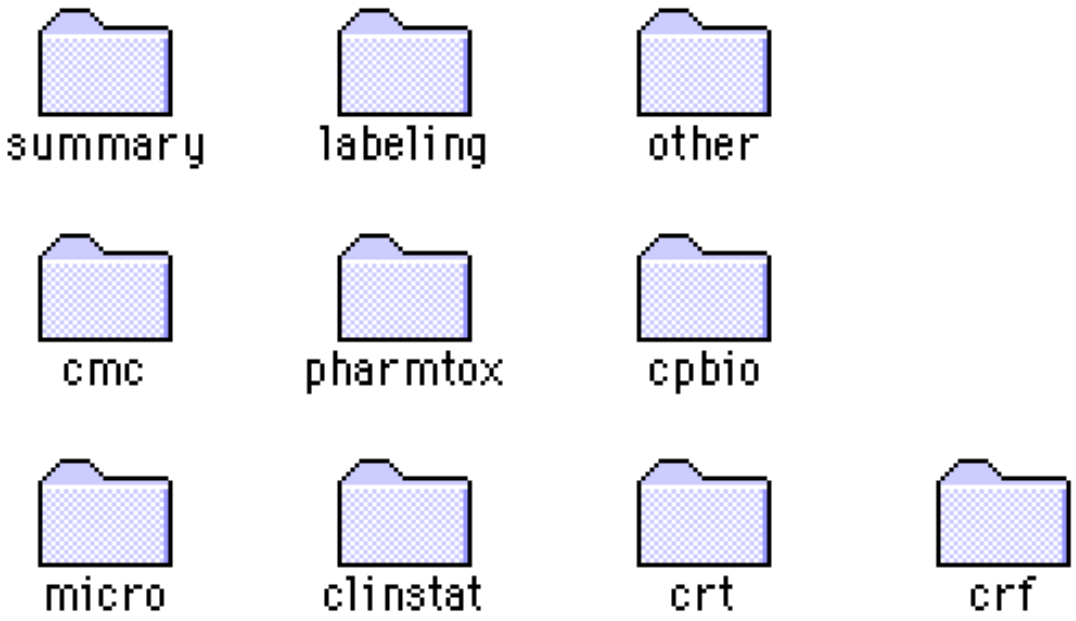
- **bookmarks for the table of contents**
- **hypertext links to references off the page**
- **identification in the document information field**

Organizing the collection of PDF files
based on items in FDA form 356h

- **Summary**
- **Labeling**
- **CMC**
- **Nonclinical pharmtox**
- **Biopharm**
- **Micro**
- **Clinstat**
- **CRT**
- **CRF**
- **Other**

Organizing the collection of PDF files

Place all files for each item in the appropriate folder


summary
labeling
other
cmc
pharmtox
cpbio
micro
clinstat
crt
crf

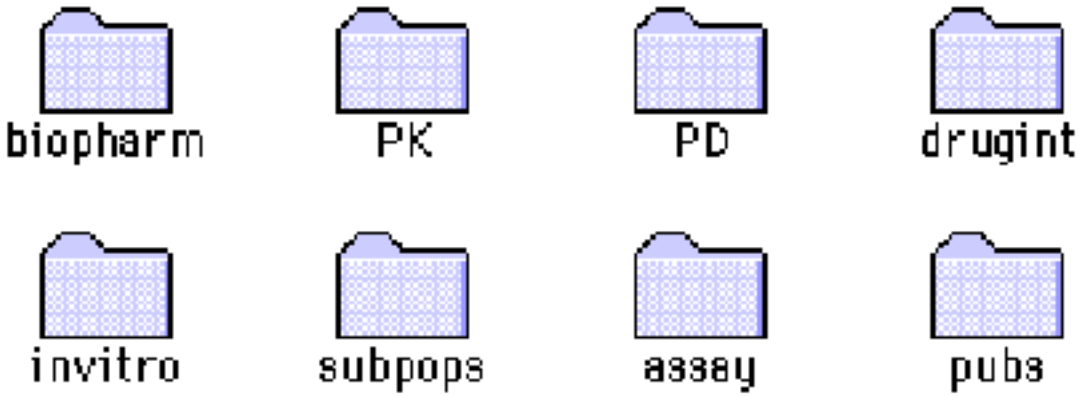
Organizing the collection of PDF files

Inside each folder may be additional subfolders

for example

CMC

For example biopharm



For each item include
A table of contents

- **list all files for the item**
- **provide a hypertext link to the appropriate file**
- **include the location of the file**
- **if a portion of the item is provided as paper include the location of the paper by volume number**

For example

Clinstat Table of Contents:

Document	Volume number	File location
Indication - Allergic Rhinitis		
Controlled trials		
Study 09	1.25	clinstat/09/09.pdf
appendices		clinstat/09/09app.pdf
Study 10	1.30	clinstat/10/10.pdf
appendices		clinstat/10/10app.pdf
Study 2001	1.35	clinstat/2001/2001.pdf
appendices		clinstat/2001/2001app.pdf

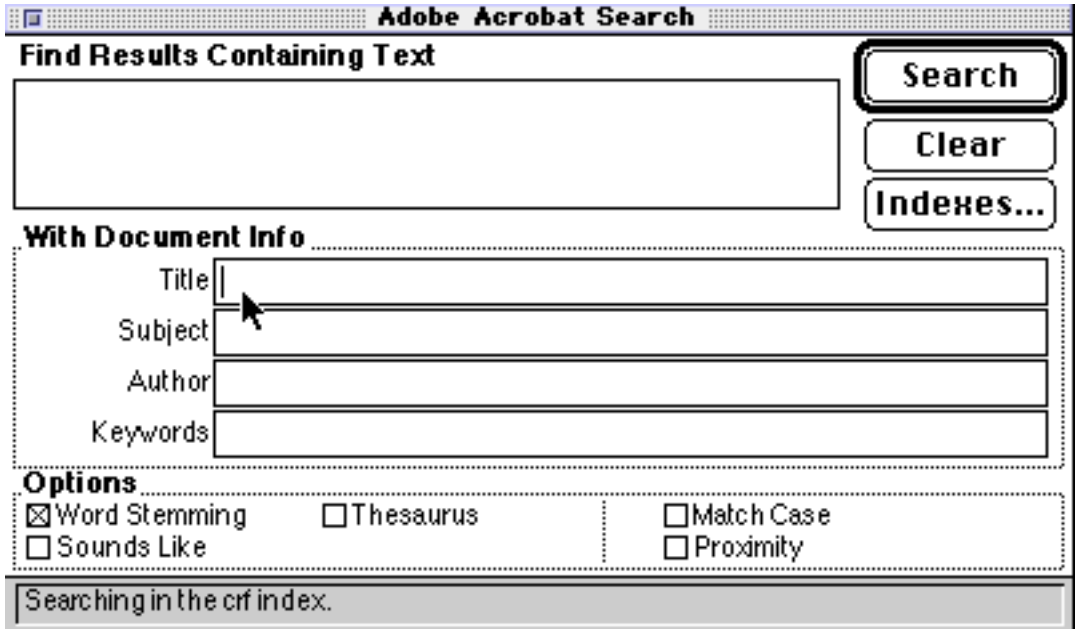
For each technical item include

A full text index

- **Don’t confuse with the table of contents**
- **Index of all words and numbers in the PDF files including the Document information fields**
- **Index consists of a index file (PDX file) and associated files contained in a single folder**

Indexing allows the reviewer to search:

- Text in a document
- Document information fields

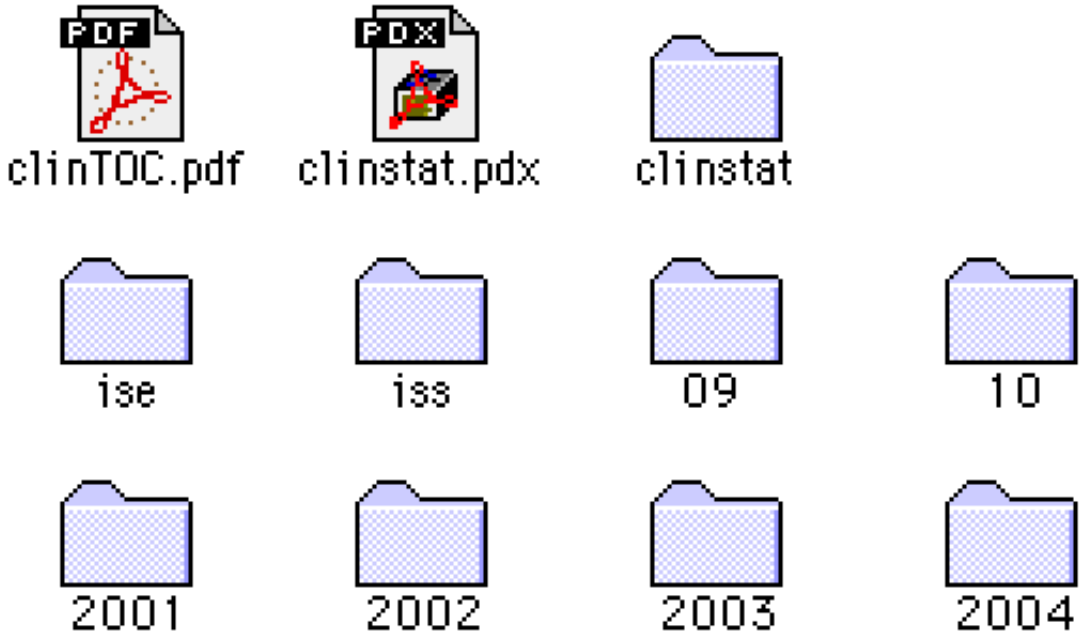


Each item contains

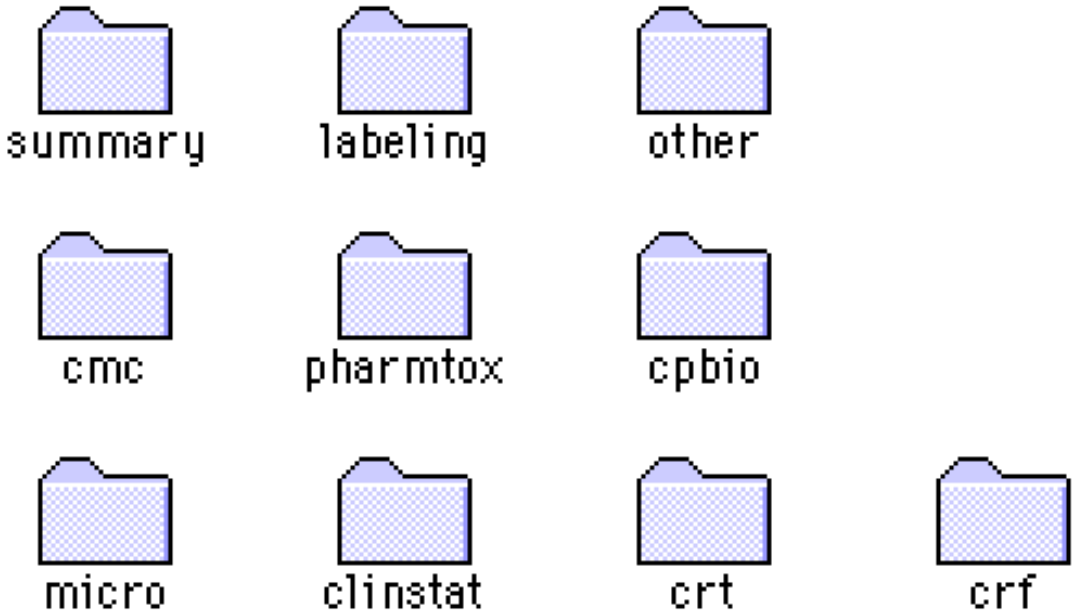
- **folder**
- **subfolders**
- **all files**
- **table of contents**
- **index**

for example

clinstat item



All items now complete



Every file and folder to be archived included in a single folder

Protects the hypertext links in the PDF files

Provide an overall Table of contents for the submission

- **Paper submission table of contents to the level of each document's table of contents**
  - **in one location, hundreds of pages**
- **Electronic submission table of contents includes same information as paper**
  - **in multiple locations, electronically linked**

Electronic table of contents includes

NDA table of contents

- **located in the main folder**
- **lists all items in the submission**
- **hypertext links to each item's table of contents**

Item's table of contents

- **located in the item's folder**
- **lists all documents in the item's folder**
- **hypertext links to each document**

Documents table of contents

- **located in the document's pdf file**
- **lists all sections and subsections of a document**
- **bookmarks link to the sections**

If submission mixture of paper and electronic documents

Must have comprehensive table of contents in both paper and electronic format with

- location of paper documents (volume number)
- location of electronic documents (path and file name)

Table of Contents for NDA 123456 (n/a = not available)			
Item	**Description**	**Paper volume number**	**Folder name**
1	**Table of contents (Index)**	**1**	**main folder**
2	**Labeling**	**n/a**	**labeling**
3	**Summary**	**n/a**	**summary**
4	**Chemistry section**	**1**	**cmc**
5	**Nonclinical pharmacology and toxicology section**	**5**	**pharmtox**
6	**Human pharmacokinetics and bioavailability section**	**n/a**	**cpbio**
7	**Clinical Microbiology**	**n/a**	**n/a**
8	**Clinical section**	**n/a**	**clinstat**
9	**Safety update report**	**n/a**	**n/a**
10	**Statistical section**	**n/a**	**clinstat**
11	**Case report tabulations**	**n/a**	**crt**
12	**Case report forms**	**n/a**	**crf**
13	**Patent information**	**n/a**	**other**
14	**Patent certification**	**n/a**	**other**
15	**Establishment description**	**n/a**	**other**
16	**Debarment certification**	**n/a**	**other**
17	**Field copy certification**	**n/a**	**other**
18	**User fee cover sheet**	**n/a**	**other**
19	**Other**	**n/a**	**other**

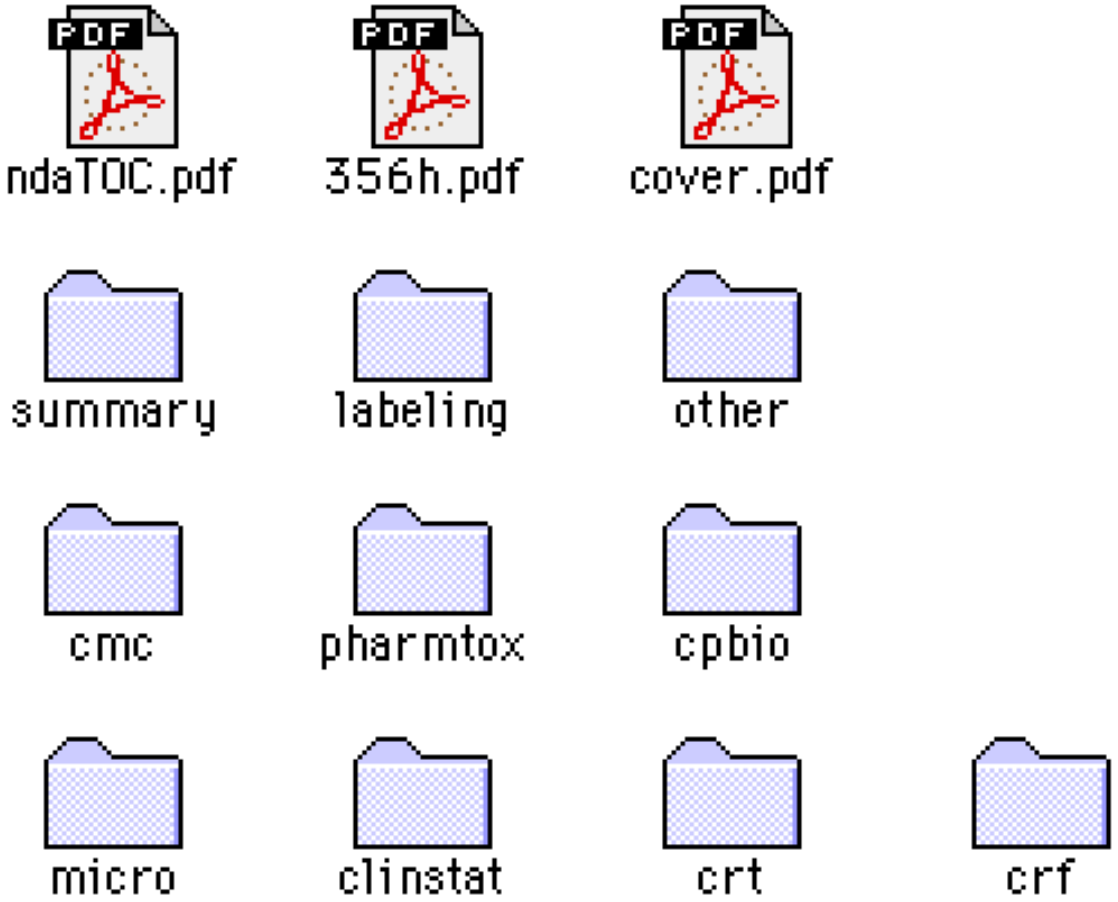
Cover letter includes
in addition to regulatory issues

- **A description of the submission**
- **A description of which portions of the submission are presented only in paper, only in electronic format, or in both paper and electronic format**
- **Verification that the submission is virus free**
- **A description of any deviation from the specifications in the guidance document.**

Provide FDA form 356h as a pdf file inside the main folder

- On page 2 of the form, note by each item if the documents for the item are in
  - paper format,
  - electronic format,
  - or both paper and electronic format

Electronic NDA



Archiving datasets
(check with reviewing division first)

SAS transport files
- **Case report tabulations**
- **Individual animal line listings**

Structured ASCII
- **CMC (in development)**
- **Biopharm (in development)**

SAS transport files

SAS transport version 5

- **processed by the XPORT engine with SAS Version 6 or 7**
- **processed by PROC XCOPY with SAS Version 5**

One data set for each domain

Possible Data Sets Files			
Background information		Results	
File name	Description	File name	Description
demog.xpt	Demographics	exposure.xpt	Drug exposure
include.xpt	Inclusion criteria	dispos.xpt	Disposition
exclude.xpt	Exclusion criteria	efficacy.xpt	Efficacy results
conmeds.xpt	Concomitant medication	adverse.xpt	Adverse Events
medhist.xpt	Medical history	lab_chem.xpt	Lab - chemistry
		lab_heme.xpt	Lab - hematology
		lab_urin.xpt	Lab - urinalysis
		ECG.xpt	ECG
		vitals.xpt	Vital signs
		exam.xpt	Physical examination

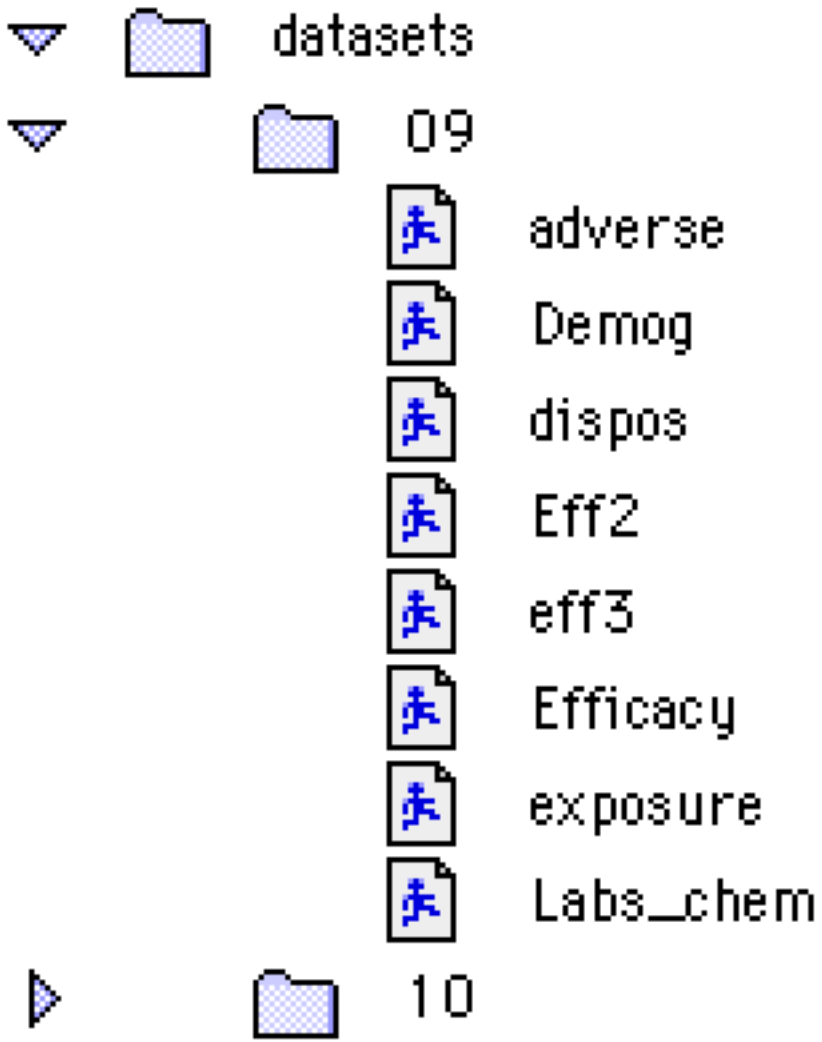
General considerations

- **Each subject should be identified with a single, unique number for the entire application.**
- **Each row should contain a single observation or result for an individual subject, allowing for multiple rows per subject.**
- **When at all possible, the same variable names and codes should be used across studies.**
- **Each data set should have patient ID, study, center/site, treatment assignment, sex, age, and/or race of the subjects.**

Organization of the data sets

- **Place all data sets in a folder with the study number**

- **Place all study folders in the datasets folder**


datasets
09
adverse
Demog
dispos
Eff2
eff3
Efficacy
exposure
Labs_chem
10

Organizing the data sets

In the dataset folder include:

Data definition table
- list of all variable names
- descriptive narrative
- data types
- codes (and decodes)

Data definition Table for Adverse Events for Study 201			
Variable name	**Narrative description**	**data type**	**Codes**
PATID	**unique patient ID number**	**number**	**n/a**
SEX	**patient's sex**	**char**	**f= female, m= male**
BDATE	**birth date**	**date**	**n/a**
TRT	**assigned treatment**	**number**	**0= placebo, 5= 5mg**

Organizing the data sets

Annotated case report form

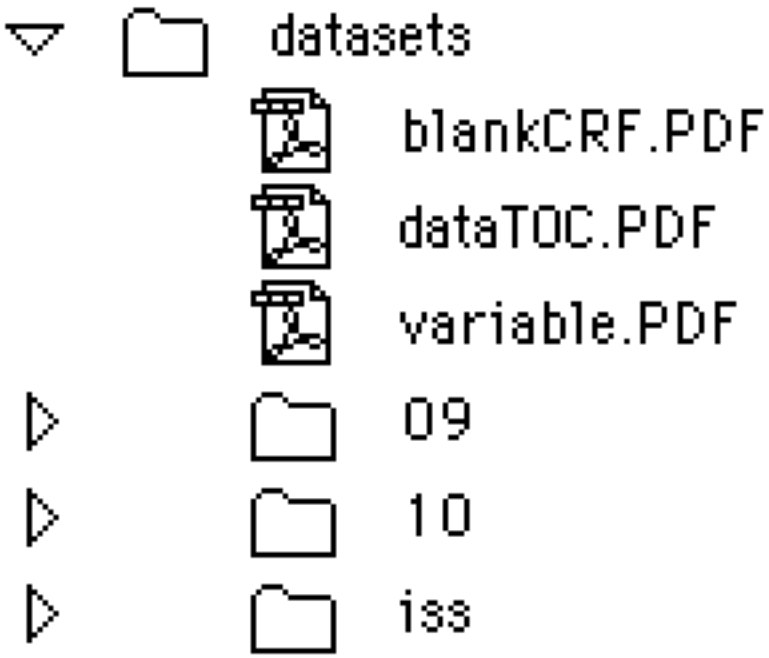
- maps each blank on the CRF to the corresponding variable in the data base
- provide
  - file names
  - variable names
  - coding

Organizing the data sets

Data sets table of contents

- list all data sets
- description of the contents
- link to data definition table for each dataset

Organizing the data sets



Special issues - Item 3

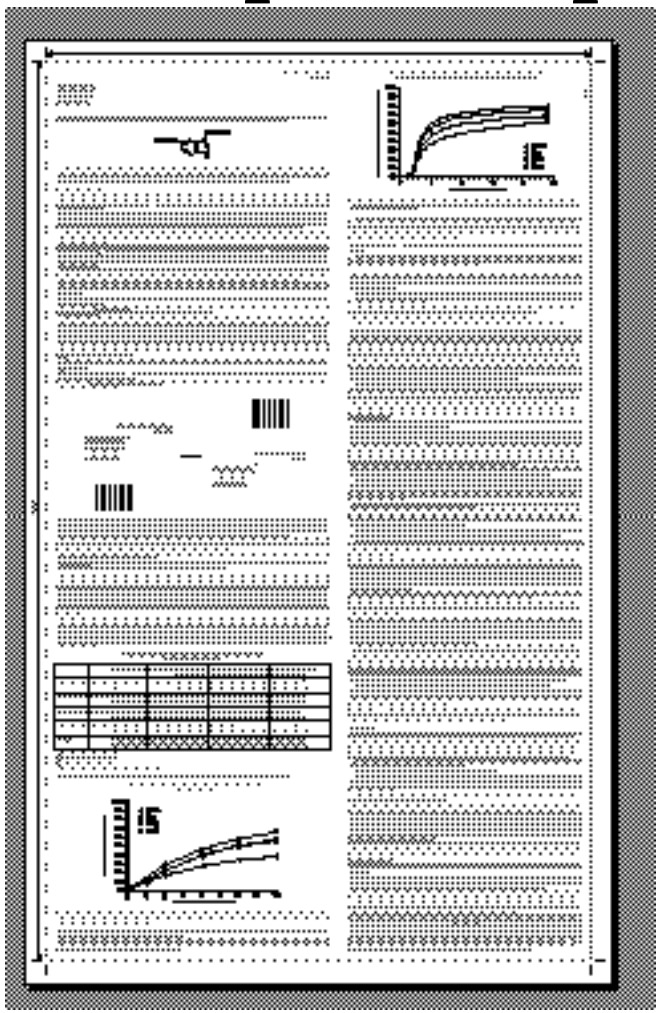
Labeling text

- content of final printed package insert
  - all text
  - all bolding
  - all tables
  - all figures

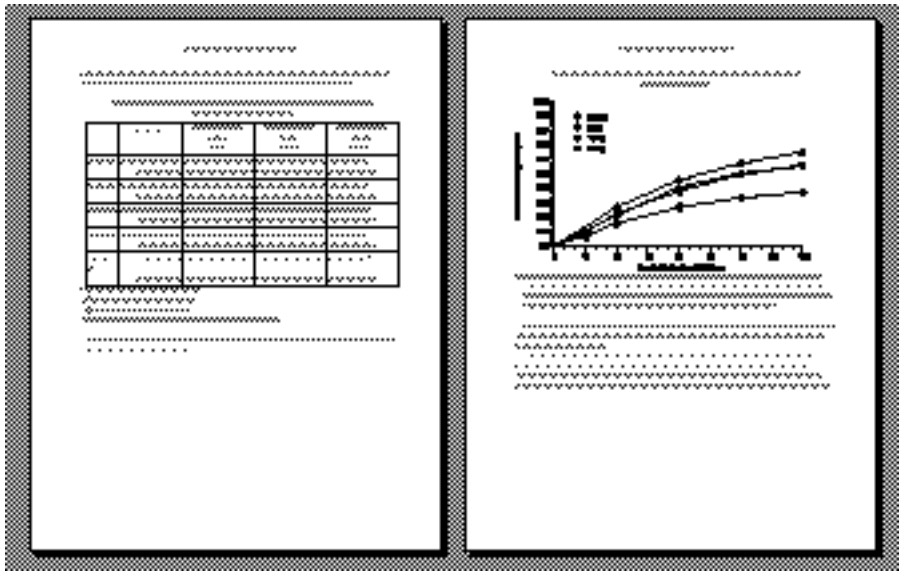
Labeling text

- format
  - 8.5 x 11 inches
  - portrait orientation
  - no columns
  - font sizes chosen for readability

Final printed package insert



Labeling text



Labeling text

in Word format

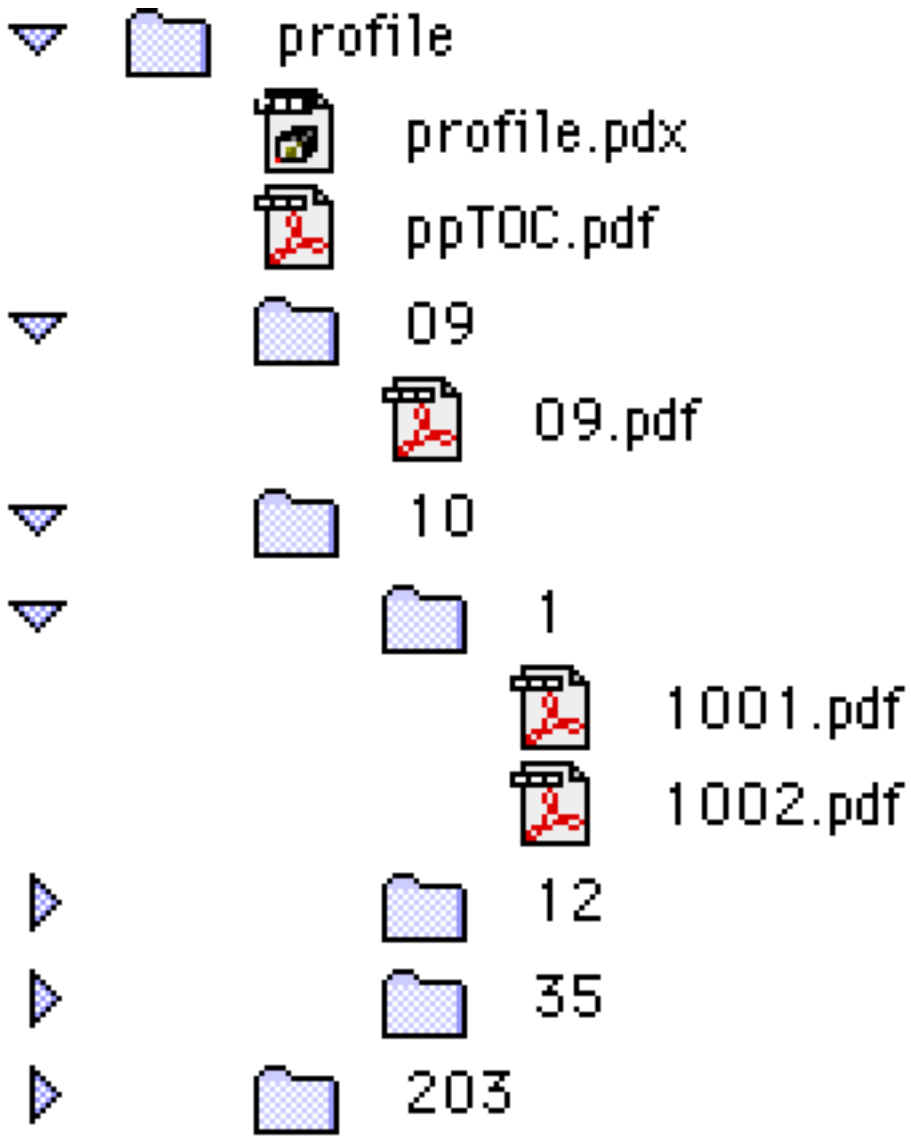
- review aid
  - editing
  - document comparison

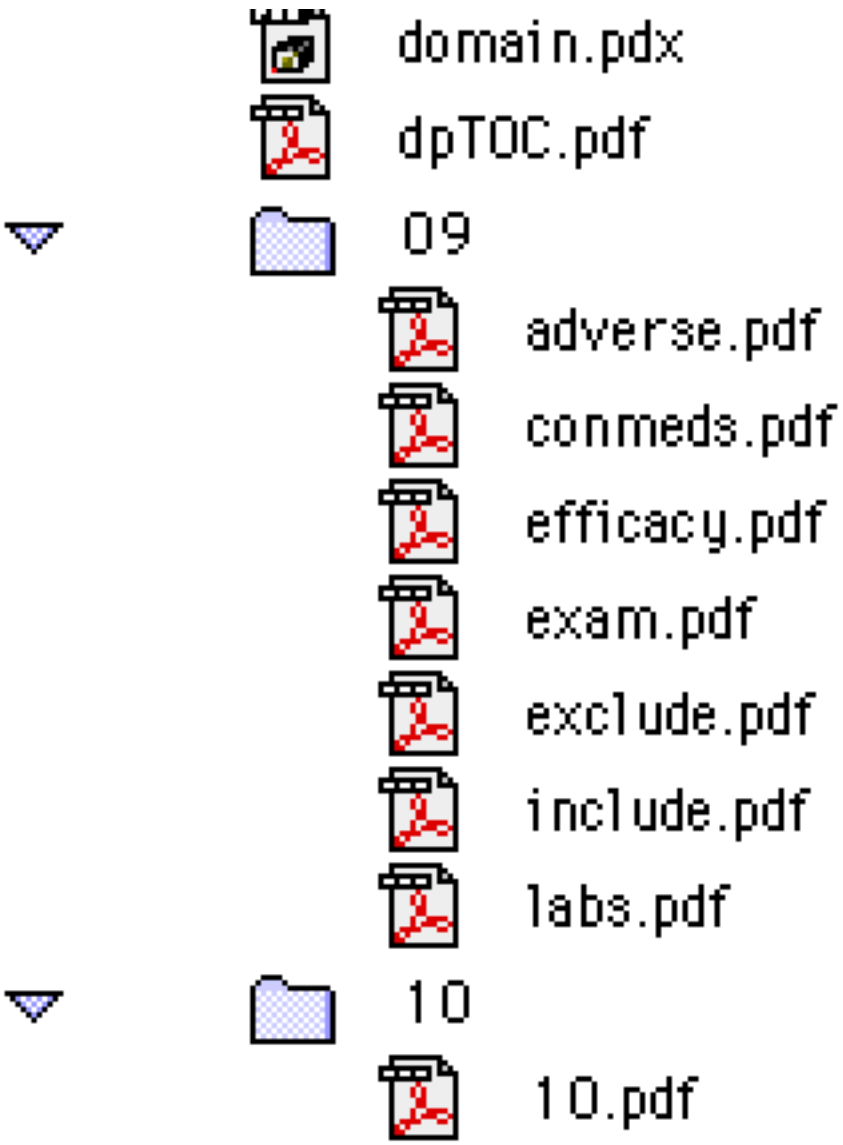
Special issues - Item 11 and 12
Case report tabulations and case report forms
Two types of CRT

Patient profiles (similar to CRF)
- all data collected for an individual patient organized by time
- format
  - PDF

Domain profile (line listings)

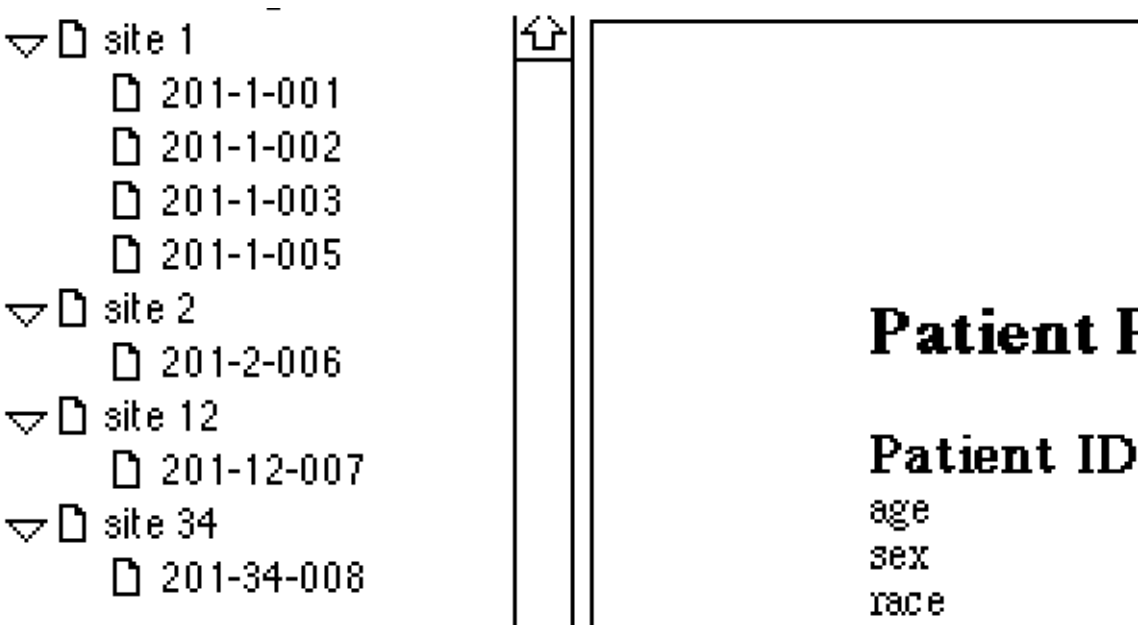
- all data collected for a single CRF domain from one study
- Format
  - PDF
  - SAS Transport


profile
profile.pdx
ppTOC.pdf
09
09.pdf
10
1
1001.pdf
1002.pdf
12
35
203


domain.pdx
dpTOC.pdf
09
adverse.pdf
conmeds.pdf
efficacy.pdf
exam.pdf
exclude.pdf
include.pdf
labs.pdf
10
10.pdf

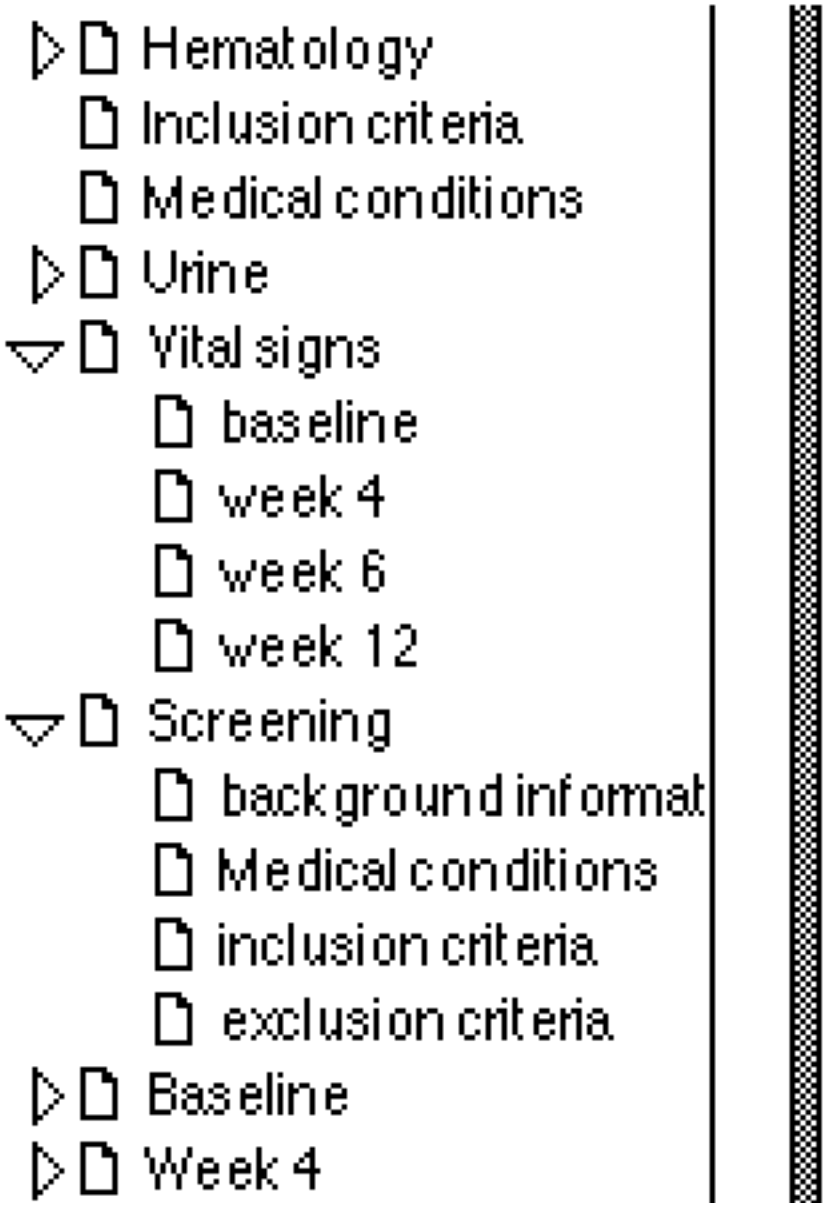
Bookmark for brief Patient profiles and CRF Example

- All patient profiles from a study in one PDF file
- Bookmarks for site and patient



Bookmark for longer Patient profiles and CRF

- **Bookmarks by study visit and/or domain (this point inadvertiently left out of draft guidance)**


Hematology
Inclusion criteria
Medical conditions
Urine
Vital signs
baseline
week 4
week 6
week 12
Screening
background informat
Medical conditions
inclusion criteria
exclusion criteria
Baseline
Week 4

Alternative to bookmarks for longer Patient profiles and CRF

- **Table of contents for each individual patient's CRFs as an alternative to bookmarks (this point inadvertiently left out of draft guidance)**

Case Report Form -example

Review copy

Format

- paper desk copy
- accurate and complete copy of the archival document
  - use the archival PDF file to generate the paper review copy

Review copy - organization

- Collection of documents
- Each document separated by volumes (or tab dividers within volumes)

Review copy table of contents

- location of each document by volume number(s)
- location of the archival PDF file by folder/file name

No paper review copy for

- assay validation reports
- individual animal line listings
- clinical study report appendices 16.1.3 to 16.4 (see ICH E3 guidelines)

Review aids

- **supplied as desk copies**
- **not considered part of the archival submission**
- **consult with CDER's Office of Information Technology (OIT) concerning any review aid that requires connection to CDER's network or may require OIT resources**
- **media based on what the review division can handle**
- **review aids sent to review division document room**